BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015233
Article Type:	Research
Date Submitted by the Author:	17-Nov-2016
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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Urology, Geriatric medicine, General practice / Family practice
Keywords:	Urinary tract infections < UROLOGY, Antibiotic prophylaxis, Antibiotic resistance

TITLE

Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials

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Abstract

Objective

To address clinical uncertainties about the effectiveness and safety of long-term antibiotic therapy for preventing recurrent UTIs in older adults.

Design

Systematic review and meta-analysis of randomised trials.

Method

We searched Medline, Embase, CINAHL and the Cochrane Register of Controlled Trials from inception to August 2016. Eligible studies compared long-term antibiotic therapy with non-antibiotic therapy or placebo in men or women aged over 65, or in postmenopausal women, with recurrent UTIs.

Results

We did not identify any studies that included older men. Three randomised controlled trials compared long-term antibiotics with vaginal oestrogens (n=150), oral lactobacilli (n=238) and D-mannose powder (n=94) in post-menopausal women. Long-term antibiotics reduced the risk of UTI recurrence by 24% (Three trials, n=482; pooled Risk Ratio (RR) 0.76; 95% confidence interval 0.61 to 0.95, NNT=8.5). There was no statistically significant increase in risk of adverse events (mild adverse events: pooled RR 1.52; 95% confidence interval 0.76 to 3.03; serious adverse events: pooled RR 0.90, 95% confidence interval 0.31 to 2.66). One trial showed 90% of urinary and faecal E coli isolates were resistant to trimethoprim-sulfamethoxazole after one month of prophylaxis.

Conclusions

Findings from three small trials with relatively short follow-up periods suggest long-term antibiotic therapy reduces the risk of recurrence in postmenopausal women with recurrent UTI. We did not identify any evidence to inform several clinically important scenarios including, benefits and harms in older men or frail care home residents, optimal duration of prophylaxis, recurrence rates once prophylaxis stops, and effects on urinary antibiotic resistance.

Strengths and limitations of this study

- Recurrent UTI is one of the most common reasons for long-term antibiotic use in the frail elderly. We systematically reviewed trial evidence to address clinical uncertainties around this practice.
- We did not identify any trials in older men.
- We identified only three small European trials, with follow-up ranging from 6 to 15 months, in older women.
- Only one trial measured the impact of long-term antibiotics on antibiotic resistance.
- Trial evidence suggests long-term antibiotics reduce the risk of UTI recurrence in older women. Many clinical uncertainties remain unaddressed.

Introduction

Older men and women are commonly prescribed long-term antibiotics to prevent recurrent urinary tract infection (UTI). [1, 2] Antibiotic use is a key driver of antibiotic resistance. [3] Therefore, antibiotic use must be justified by robust evidence, where the estimated benefit outweighs estimated harm.

UTIs, and consequently recurrent UTIs, are over-diagnosed in older people.[4, 5] Therefore, antibiotic prophylaxis may actually be prescribed for symptoms that represent bladder dysfunction or localised vaginal symptoms rather than true UTI, and thus will not confer the intended benefit. Multi-morbidity, frailty and polypharmacy are more common in older people and are contributory factors for potential harms such as those related to drug interactions. For example, older adults co-prescribed renin-angiotensin system inhibitors and trimethoprim-containing antibiotics were shown to be at increased risk of hyperkalaemia related hospitalisation [6] and sudden death.[7]

Previous meta-analyses showed antibiotic prophylaxis conferred a relative risk reduction of 79% in the proportion of women experiencing a microbiologically confirmed UTI, compared to placebo.[8] However, these analyses included data from mostly small trials of younger women without co-morbidities. There is uncertainty around the generalizability of these findings to older adults.

There are several important clinical uncertainties relating to long-term antibiotic use in older adults with recurrent UTI, including effect on frequency of infective episodes, optimal duration of prophylaxis, adverse effects, risk of relapse following cessation of prophylaxis and effect on urinary antibiotic resistance. We therefore systematically

reviewed randomised controlled trials comparing long-term antibiotic prophylaxis with placebo or non-antibiotic therapy for preventing further episodes of UTI in older people. Our main objective was to quantify the benefits and harms of long-term antibiotics for older adults, to better inform patients and clinicians during clinical decision-making.

Methods

We conducted a systematic review following guidance from the Cochrane handbook for systematic reviews of interventions for conduct and PRISMA guidelines for reporting.[9] The review protocol was prospectively registered on PROSPERO; (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016628) Registration number: PROSPERO 2015:CRD42015016628).

Data sources

We systematically searched Medline, Embase, CINAHL and the Cochrane Central Register of Controlled Trials from inception to March 2016 for English language randomised controlled trials. Our search strategy consisted of keywords and MESH terms for urinary tract infection and randomised trials (appendix 1).

One author (HA) conducted the first screening of potentially relevant records based on titles and abstracts and two authors (HA and FD) independently performed the final selection of included trials based on full text evaluation. Reference lists of included studies and relevant systematic reviews were screened for further potentially relevant studies. Disagreements between the two reviewers were resolved through discussion.

Study selection

We included only randomised controlled trials published in full (i.e., not abstracts) in English, comparing the effect of long-term antibiotics versus placebo or non-antibiotic interventions on the rate of UTI in older adults with recurrent UTI. We defined “long-term antibiotics” as daily antibiotic dosing for at least six months, “older adults” as women who were postmenopausal or over the age of 65, and men aged over 65 and “recurrent UTI” as self-reported or clinically recorded history of two or more UTIs in six months, or three or more in 12 months.

We included studies recruiting adults of all ages and screened relevant results to assess whether reported data allowed estimates of effect size in our specified population of older adults. For data not presented in this format, we contacted authors if the study was published in the last ten years and if the mean or median age in any arm was greater than 50 years.

We excluded studies evaluating the effect of prophylactic antibiotics in specific situations, e.g., post catheterisation, post-surgery, in patients with spinal injuries or in those with structural renal tract abnormalities.

Outcome measures

Our primary outcome was the number of urinary tract infection recurrences per patient year during the prophylaxis period, defined microbiologically (>100,000 colony forming units of bacteria/ml of urine) and/or clinically (for example, dysuria, polyuria, loin pain, fever), or other measure of change in the frequency of UTI events during prophylaxis. We also aimed to assess the proportion of patients with severe (requiring withdrawal of treatment) and mild (not requiring withdrawal of treatment) adverse effects. Secondary outcomes included the proportion of patients who experienced at least one recurrence after the prophylaxis period, time to first

recurrence, proportion of patients with antibiotic resistant micro-organisms in future urine samples, and quality of life.

Data extraction and quality assessment

One reviewer (HA) extracted study characteristics (setting, participants, intervention, control, funding source) and outcome data from included trials. We contacted two authors for sub-group data on postmenopausal women. One author replied and provided relevant outcome data. Two reviewers (HA and SP) independently assessed the risk of bias of the included studies using the Cochrane Collaboration's risk of bias tool.[10] Disagreements were resolved through discussion. We used RevMan version 5.3 to meta-analyse the data and generate forest plots.

Data synthesis and analysis

Outcomes measured in only one trial were reported narratively. Outcomes measured in more than one trial were synthesised quantitatively. We estimated between trial heterogeneity using the I^2 statistic [11] and used random effects meta-analyses to estimate pooled risk ratios and 95% confidence intervals. [12] We undertook sensitivity analyses to examine treatment effects according to study quality and assessed the impact of including data from a potentially eligible trial where the study author did not reply to our request for data on older participants.

Results

From 6645 records, we identified 53 studies for full-text review (See Appendix 1). Four studies were eligible for inclusion.[13-16] Two studies recruited only postmenopausal women.[15, 16] Two studies recruited women of all ages but the

median age was >50 years.[13, 14] For these studies, we contacted authors requesting data for postmenopausal women, or if menopausal status not ascertained, for women aged over 65. We received data from one author and hence included three trials consisting of 534 postmenopausal women in our review (Table 1).[14-16] We did not identify any studies that included older men.

Study ID	Setting	Population	Intervention	Control	Confirmation of UTI	Outcomes
Raz 2003	Outpatient infection disease clinics in Northern Israel	Community dwelling postmenopausal women with recurrent UTI[+]	Nitrofurantoin 100mg capsule at night for 9 months, with placebo vaginal pessary to mimic control group	Vaginal pessary containing 0.5mg Estriol daily for two weeks, then once a fortnight for nine months, with oral placebo capsules at night to mimic the intervention group	$>10^3$ colony forming units/mL bacteria in midstream urine	1.Number of women experiencing a recurrence during the prophylaxis period 2.Mean number of UTIs per woman during the prophylaxis period 3.Effects of oestrogens and antibiotics on vaginal mucosa, flora and pH 4.Mild and serious adverse events
Beerepoot 2012	Community setting in Amsterdam	Community dwelling postmenopausal women with a self-reported history of at least 3 UTIs in the preceding year	Trimethoprim-sulfamethoxazole 480mg tablet at night for 12 months, with placebo capsule twice daily	One capsule containing at least 10^9 colony forming units of *L rhamnosus GR-1* and *L reuteri RC-14* twice daily for 12 months, with placebo capsule at night	Symptoms +/- $>10^3$ colony forming units/mL bacteria in midstream urine	1.Number of women experiencing a recurrence during, and three months after the prophylaxis period 2.Mean number of UTIs per woman during the prophylaxis period 3.Median time to first recurrence during and after the prophylaxis period 4.Effects of lactobacilli and antibiotics on vaginal flora 5.Effects of lactobacilli and antibiotics on urinary and faecal antibiotic resistance 6.Mild and serious adverse events
Kranjcec 2014	Outpatients and primary care in Zabok, Croatia	Community dwelling women with self-reported recurrent UTI[+]	Nitrofurantoin 50mg at night for six months	Two grams D-mannose powder diluted in 200mls water at night for six months OR No treatment	Symptoms and $>10^3$ colony forming units/mL bacteria in midstream urine	1.Number of women experiencing a recurrence during the prophylaxis period 2.Median time to first recurrence during the prophylaxis period 3.Adverse events

Table1. Characteristics of included studies

† defined as two confirmed episodes of uncomplicated UTI in six months, or three in twelve months.

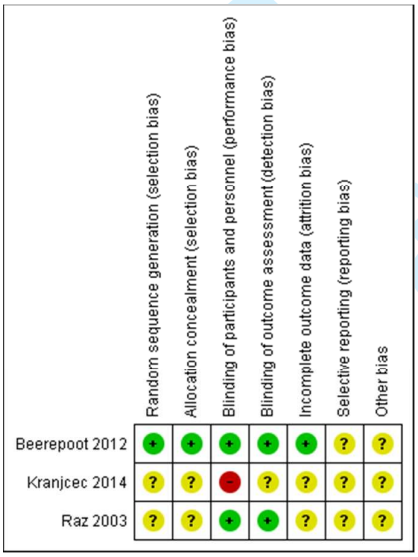
Trial characteristics

Trials were conducted in community and outpatient settings in Israel, Netherlands and Croatia. Intervention arms consisted of 6 to 12 months of antibiotic therapy. Control arms consisted of non-antibiotic prophylaxis with vaginal oestrogen pessaries[15], oral lactobacilli capsules[16], and D-mannose powder.[14] One trial reported the number of urinary tract infection recurrences per patient year during the prophylaxis period.[16] All trials reported the number of women experiencing a UTI during the prophylaxis period and frequency of adverse events. Only one trial assessed recurrence of UTI after the prophylaxis period (3 months).[16] One trial assessed effect on urinary and faecal bacterial resistance.[16]

Risk of bias

Figure 1 summarises the risk of bias assessment. Allocation and randomisation details were poorly reported in two trials.[14,15] One trial was assessed as high risk for performance and detection bias; trial arms consisted of an oral antibiotic capsule or D-mannose powder diluted in 200mls water or no treatment with no use of placebo and did not report on blinding of outcome assessors. [14] Only one trial reported a sample size calculation.[14] Overall, one trial was judged to be low risk of bias [16] and two trials unclear risk due to limited reporting of methods.[14,15]

Figure 1. Summary of risk of bias assessment



Effect of long-term antibiotics on recurrent UTI

Compared to a capsule of Lactobacilli, prophylaxis with 480mg of trimethoprim-sulfamethoxazole for 12 months led to fewer microbiologically confirmed UTI episodes per patient year (mean number of episodes per year = 1.2 versus 1.8, mean difference 0.6 , 95% confidence interval 0.0 to 1.4, *p*=0.02). Prophylaxis with trimethoprim-sulfamethoxazole also led to less women experiencing a microbiologically confirmed UTI during prophylaxis (49.4% versus 62.9%; RR 0.79, 95% confidence interval 0.63 to 1.0), and an increase in time to first UTI (six months versus three months; log-rank *p*=0.02). There was no difference between arms in the mean number of microbiologically confirmed UTI episodes three months after

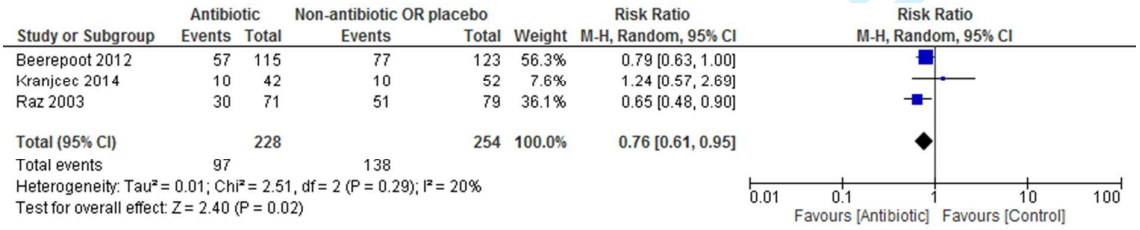
cessation of prophylaxis (mean number of episodes = 0.1 versus 0.2, mean difference 0.0, 95% confidence interval -0.1 to 0.3, *p*=0.64). [16]

Compared to vaginal oestrogen pessaries, prophylaxis with 100mg of nitrofurantoin for nine months led to fewer women experiencing a UTI during prophylaxis (42.3% versus 64.6%; RR 0.65, 95% confidence interval 0.8 to 0.90), and a lower mean number of UTI's per woman (0.6 episodes per woman versus 1.6 episodes per woman).[15]

Compared to D-mannose powder prophylaxis with 50mg of nitrofurantoin for six months led to more postmenopausal women experiencing a UTI during prophylaxis (24% versus 19%, RR 1.24, 95% confidence interval 0.57 to 2.69).[14]

Random effects meta-analysis (figure 2) shows long-term antibiotic therapy reduces the risk of a woman experiencing a UTI during the prophylaxis period (pooled Risk Ratio 0.76; 95% confidence interval 0.61 to 0.95) with about eight post-menopausal women needing treatment with long-term antibiotics to prevent one woman experiencing a UTI during the prophylaxis period (NNT=8.5).

Figure 2. Forest plot showing results of meta-analysis for proportion of women experiencing a UTI during the prophylaxis period.



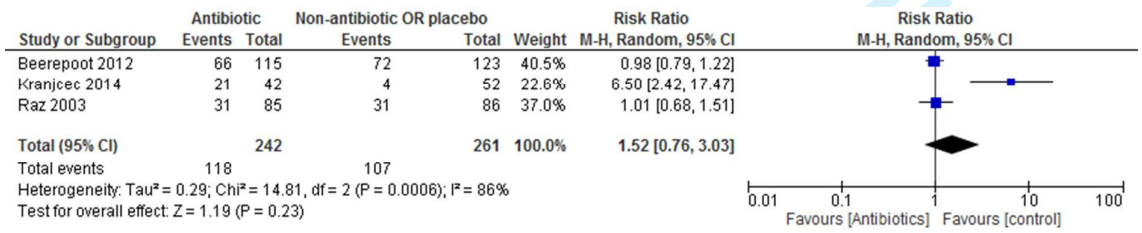
Adverse events

Commonly reported side effects across the three trials included skin rash, gastrointestinal disturbance and vaginal symptoms. There were no statistically significant difference between odds of adverse events between trimethoprim-sulfamethoxazole and lactobacilli [16], or between nitrofurantoin and vaginal oestrogens. [15] Risk of side effects with D-mannose powder was significantly lower than with nitrofurantoin (RR 0.28; 95% confidence interval 0.13 to 0.57).[14] Overall, absolute numbers of serious adverse events or events resulting in treatment withdrawal were small.

We had data on mild adverse events (not resulting in treatment withdrawal) for all three trials. There was marked heterogeneity between trials for adverse events (I^2 = 86%).

Meta-analyses showed no statistically significant difference between antibiotics and control for overall risk of mild adverse events (pooled RR 1.52; 95% confidence interval 0.76 to 3.03) (figure 3).

Figure 3. Forest plot showing results of meta-analysis for proportion of women experiencing mild side effect (treatment not withdrawn) during the prophylaxis period.



We extracted data for serious adverse events (resulting in treatment withdrawal) for two trials. Meta-analyses showed no statistically significant difference between

antibiotics and control for overall risk of serious adverse events (pooled RR 0.90; 95% confidence interval 0.31 to 2.66; figure 4).

Figure 4. Forest plot showing results of meta-analysis for proportion of women experiencing a serious side effect (resulting in treatment withdrawal) during the prophylaxis period.

Effect of long-term antibiotic therapy on bacterial resistance

Compared with lactobacilli, women receiving 12 months prophylaxis with trimethoprim-sulfamethoxazole showed dramatic increases in the proportion of antibiotic resistant bacteria isolated from urine and faeces. For example, 20-40% of urinary and faecal E coli isolates were resistant to trimethoprim-sulfamethoxazole, trimethoprim and amoxicillin at baseline, increasing to 80-95% after one month of treatment. Over the 15 month follow-up period, resistance levels decreased following cessation of prophylaxis but remained above baseline levels.[16]

Sensitivity analyses

We assessed the impact of removing the study at high risk of bias on effect size and direction.[14] Removal made little difference to the meta-analysis for proportion of women experiencing a UTI during the prophylaxis period (pooled RR 0.74; 95% confidence interval 0.61 to 0.89). Removal did impact on the meta-analysis for proportion of women experiencing mild side effects during the prophylaxis period but

overall difference between antibiotics and placebo did not reach statistical significance (pooled RR 0.99, 95% confidence interval 0.82 to 1.20).

We also pooled aggregate data from another potentially relevant study where authors did not respond to our request for data regarding postmenopausal women/women over 65.[13] This study compared 500mg of cranberry extract to 100mg trimethoprim taken at night for six months. However, adding aggregate data for the whole study population (women aged 45 and above) to our meta-analysis for the proportion of women experiencing a UTI during the prophylaxis period made little difference to risk estimates (pooled RR 0.74; 95% confidence interval 0.61 to 0.90).

Discussion

Summary

This systematic review assessed evidence from three European randomised trials reported between 2003 and 2014. Trials only included women. Compared to controls, long-term prophylaxis with antibiotics reduced the risk of postmenopausal women experiencing a recurrent UTI during the prophylaxis period, without a statistically significant increase in risk of adverse events. Data from one trial [16] suggested this benefit was limited to duration of prophylaxis and was not apparent three months after cessation of prophylactic treatment. Data from one trial[16] showed long-term antibiotic prophylaxis dramatically increased urinary and faecal antibiotic resistance. However, trials were small with relatively short follow-up and had limitations in design and reporting, with one trial judged high risk for bias.

Strengths and limitations

We conducted this review following prospective registration of a review protocol and in line with guidance from the Cochrane handbook for systematic reviews of interventions. Our search strategies was comprehensive and supplemented with reviews of reference lists of relevant trials[13-16], systematic reviews [8, 17, 18] and clinical guidelines. [19-21] We contacted authors where additional data were required for study inclusion. Due to resource constraints, we limited searches to English language and may have missed potentially relevant studies.

Comparison with existing literature

Meta-analysis of 10 randomised trials of women aged 18 and older found long-term antibiotics reduced the risk of UTI recurrence during the prophylaxis period by almost 80% (RR 0.21; 95% confidence interval 0.13 to 0.34; NNT = 1.85).[8] Our analyses showed a smaller effect size and greater NNT for postmenopausal women, possibly due to more complex pathophysiology of recurrent UTI in this population. We did not identify a statistically significant increase in risk of adverse events associated with use of antibiotics. Adverse events are often poorly reported in trials,[22] and we found heterogeneity for adverse events between trials. In addition, the studies included in this review compared long-term antibiotic therapy with various non-antibiotic treatments and not placebo, and this may have influenced effect sizes for adverse events towards the null. We found small absolute numbers of serious adverse events, and cannot exclude the possibility of important effects being missed in these relatively small studies.

During two point prevalence surveys, almost half of all adults residing in a sample of care homes were prescribed antibiotics for prevention of recurrent UTI.[1, 2] Based on three small trials, with relatively short follow-up periods and design limitations, our

meta-analyses suggest that this widely practiced use of prophylaxis reduces risk of recurrence in women. However, it is still unclear if these benefits extend to older men or frailer care home populations. These are important gaps in current evidence, especially given large-scale observational data showing 10% of older men who experience an acute UTI go on to have at least one recurrence. [23]

Only one study followed up participants after cessation of prophylaxis and found that beneficial effects had ceased after 3 months.[16] Previous studies of younger women have reported similar findings suggesting that prophylaxis only confers protection from recurrence during the active prophylaxis phase.[8]

We found little data on the impact of long-term antibiotic therapy on antibiotic resistance. Antibiotic use is associated with increased risk of resistance.[3] Given the potential harms from acquiring an antibiotic resistant infection, the risk inferred by long-term antibiotic use is an important factor to consider with patients when making decisions about antibiotic prophylaxis.

Implications for research and practice

Based on the data we analysed, a pragmatic approach is required when considering prescribing long-term antibiotics in older patients with recurrent UTI. Although long-term antibiotics may reduce the risk of UTI recurrence in women, this benefit diminishes upon cessation of treatment. Little is known about optimal prophylaxis period, long-term effects on health, risk of antibiotic resistant infections, effects in older men, or impact on important patient centred outcomes. These unknowns need to be balanced against benefits and patient preferences.

Future research efforts on recurrent UTI should focus on improving the design and reporting of trials and developing a core set of outcomes to allow better synthesis of

trial data. Antibiotic prophylaxis should be compared with non-antibiotic prophylaxis with some evidence of efficacy (such as vaginal oestrogens) rather than those with little or poor evidence of efficacy. Researchers should address unanswered questions regarding long-term effects, duration of use, adverse effects and antibiotic resistance.

Conclusion

There is no data to inform prescribing of long-term antibiotics to older men with recurrent UTI. Prescribing long-term antibiotics to older women with recurrent UTI needs careful discussion between patient and clinician of reduced risk of relapse, potential increases in urinary and faecal antibiotic resistance and rapidly diminished benefit once prophylaxis stops.

Acknowledgements

We thank Bojana Kranjčec, Dino Papeš, and Silvio Altarac for providing requested data.

Funding

This report is independent research arising from a National Institute of Health Research (NIHR) Doctoral Research Fellowship awarded to Haroon Ahmed, and supported by Health and Care Research Wales (HCRW). The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS Wales, HCRW or the Welsh Government. The funders had no role in the design or preparation or this manuscript.

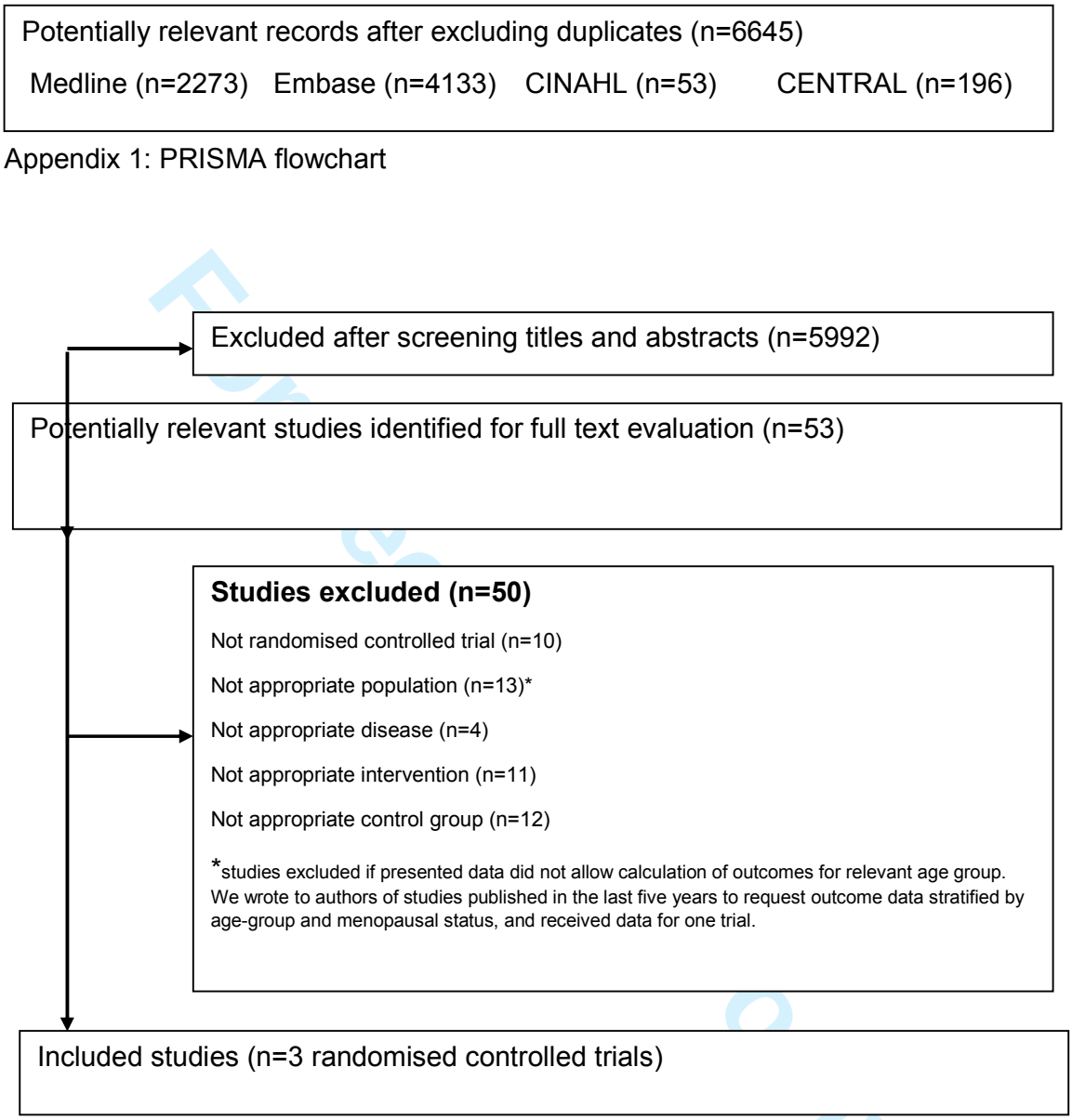
Competing interests

All authors have completed the ICMJE uniform disclosure form atwww.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might

have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Author contributions

HA, CB, NF, DF and SP conceived and designed the study. HA and FD did the searches. HA, FD and SP assessed studies for inclusion and risk of bias and extracted relevant data. HA wrote the first draft of the manuscript. All authors contributed to further drafts and final manuscript.



Appendix 1: PRISMA flowchart

Appendix 2. Medline Search strategy

1. exp Urinary Tract Infections/

2. Urinary Tract Infection*.mp.

3. exp Cystitis/

4. (bladder adj infection*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

5. Bacteriuria.mp.

6. Pyuria.mp.

7. (recurrent adj urinary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

8. UTI.mp.

9. exp Anti-Bacterial Agents/ or exp Antibiotic Prophylaxis/

10. antimicrobial*.mp.

11. randomized controlled trial.pt.

12. controlled clinical trial.pt.

13. randomized.ab.

14. placebo.ab.

15. clinical trials as topic.sh.

16. randomly.ab.

17. trial.ti.

18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

19. 9 or 10

20. 18 and 19

21. 11 or 12 or 13 or 14 or 15 or 16 or 17

22. exp animals/ not humans.sh.

23. 21 not 22

24. 20 and 23

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Text S1 - Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3 and 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix2

Section/topic	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Appendix1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Figure1 page 11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and	12-14

Section/topic	#	Checklist item	Reported on page #
		confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure1 page 11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression) (see Item 16).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING1			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

BMJ Open

Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015233.R1
Article Type:	Research
Date Submitted by the Author:	28-Jan-2017
Complete List of Authors:	Ahmed, Haroon; Cardiff University School of Medicine, Division of Population Medicine Davies, Freya; Cardiff University School of Medicine, Division of Population Medicine Francis, Nick A.; Cardiff University School of Medicine, Division of Population Medicine Farewell, Daniel; Cardiff University School of Medicine, Division of Population Medicine Butler, Christoper; University of Oxford, Department of Primary Care Health Sciences Paranjothy, Shantini; Cardiff University School of Medicine, Division of Population Medicine
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Urology, Geriatric medicine, General practice / Family practice
Keywords:	Urinary tract infections < UROLOGY, Antibiotic prophylaxis, Antibiotic resistance

TITLE

Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials

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Abstract

Objective

To address clinical uncertainties about the effectiveness and safety of long-term antibiotic therapy for preventing recurrent UTIs in older adults.

Design

Systematic review and meta-analysis of randomised trials.

Method

We searched Medline, Embase, CINAHL and the Cochrane Register of Controlled Trials from inception to August 2016. Eligible studies compared long-term antibiotic therapy with non-antibiotic therapy or placebo in men or women aged over 65, or in postmenopausal women, with recurrent UTIs.

Results

We did not identify any studies that included older men. Three randomised controlled trials compared long-term antibiotics with vaginal oestrogens (n=150), oral lactobacilli (n=238) and D-mannose powder (n=94) in post-menopausal women. Long-term antibiotics reduced the risk of UTI recurrence by 24% (Three trials, n=482; pooled Risk Ratio (RR) 0.76; 95% confidence interval 0.61 to 0.95, NNT=8.5). There was no statistically significant increase in risk of adverse events (mild adverse events: pooled RR 1.52; 95% confidence interval 0.76 to 3.03; serious adverse events: pooled RR 0.90, 95% confidence interval 0.31 to 2.66). One trial showed 90% of urinary and faecal E coli isolates were resistant to trimethoprim-sulfamethoxazole after one month of prophylaxis.

Conclusions

Findings from three small trials with relatively short follow-up periods suggest long-term antibiotic therapy reduces the risk of recurrence in postmenopausal women with recurrent UTI. We did not identify any evidence to inform several clinically important scenarios including, benefits and harms in older men or frail care home residents, optimal duration of prophylaxis, recurrence rates once prophylaxis stops, and effects on urinary antibiotic resistance.

Strengths and limitations of this study

- Recurrent UTI is one of the most common reasons for long-term antibiotic use in the frail elderly. We systematically reviewed trial evidence to address clinical uncertainties around this practice.
- We did not identify any trials in older men, nor any trials in frail care home residents.
- We identified only three small European trials, with follow-up ranging from 6 to 15 months, in older women.
- Only one trial measured the impact of long-term antibiotics on antibiotic resistance.
- Trial evidence suggests long-term antibiotics reduce the risk of UTI recurrence in older women. Many clinical uncertainties remain unaddressed.

Introduction

Older men and women are commonly prescribed long-term antibiotics to prevent recurrent urinary tract infection (UTI). [1 2] Antibiotic use is a key driver of antibiotic resistance. [3] Therefore, antibiotic use must be justified by robust evidence, where the estimated benefit outweighs estimated harm.

UTIs, and consequently recurrent UTIs, are over-diagnosed in older people.[4 5] Therefore, antibiotic prophylaxis may actually be prescribed for symptoms that represent bladder dysfunction or localised vaginal symptoms rather than true UTI, and thus will not confer the intended benefit. Multi-morbidity, frailty and polypharmacy are more common in older people and are contributory factors for potential harms such as those related to drug interactions. For example, older adults co-prescribed renin-angiotensin system inhibitors and trimethoprim-containing antibiotics were shown to be at increased risk of hyperkalaemia related hospitalisation [6] and sudden death.[7]

Previous meta-analyses showed antibiotic prophylaxis conferred a relative risk reduction of 79% in the proportion of women experiencing a microbiologically confirmed UTI, compared to placebo.[8] However, these analyses included data from mostly small trials of younger women without co-morbidities. There is uncertainty around the generalizability of these findings to older adults.

There are several important clinical uncertainties relating to long-term antibiotic use in older adults with recurrent UTI, including effect on frequency of infective episodes, optimal duration of prophylaxis, adverse effects, risk of relapse following cessation of

prophylaxis and effect on urinary antibiotic resistance. We therefore systematically reviewed randomised controlled trials comparing long-term antibiotic prophylaxis with placebo or non-antibiotic therapy for preventing further episodes of UTI in older people. Our main objective was to quantify the benefits and harms of long-term antibiotics for older adults, to better inform patients and clinicians during clinical decision-making.

Methods

We conducted a systematic review following guidance from the Cochrane handbook for systematic reviews of interventions for conduct and PRISMA guidelines for reporting.[9] The review protocol was prospectively registered on PROSPERO; (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016628) Registration number: PROSPERO 2015:CRD42015016628).

Data sources

We systematically searched Medline, Embase, CINAHL and the Cochrane Central Register of Controlled Trials from inception to March 2016 for English language randomised controlled trials. Our search strategy consisted of keywords and MESH terms for urinary tract infection and randomised trials (appendix 1).

One author (HA) conducted the first screening of potentially relevant records based on titles and abstracts and two authors (HA and FD) independently performed the final selection of included trials based on full text evaluation. Reference lists of included studies and relevant systematic reviews were screened for further potentially relevant studies. Disagreements between the two reviewers were resolved through discussion.

Study selection

We included only randomised controlled trials published in full (i.e., not abstracts) in English, comparing the effect of long-term antibiotics versus placebo or non-antibiotic interventions on the rate of UTI in older adults with recurrent UTI. We defined “long-term antibiotics” as daily antibiotic dosing for at least six months, “older adults” as women who were postmenopausal or over the age of 65, and men aged over 65 and “recurrent UTI” as self-reported or clinically recorded history of two or more UTIs in six months, or three or more in 12 months.

We included studies recruiting adults of all ages and screened relevant results to assess whether reported data allowed estimates of effect size in our specified population of older adults. For data not presented in this format, we contacted authors if the study was published in the last ten years and if the mean or median age in any arm was greater than 50 years.

We excluded studies evaluating the effect of prophylactic antibiotics in specific situations, e.g., post catheterisation, post-surgery, in patients with spinal injuries or in those with structural renal tract abnormalities.

Outcome measures

Our primary outcome was the number of urinary tract infection recurrences per patient year during the prophylaxis period, defined microbiologically (>100,000 colony forming units of bacteria/ml of urine) and/or clinically (for example, dysuria, polyuria, loin pain, fever), or other measure of change in the frequency of UTI events during prophylaxis. We also aimed to assess the proportion of patients with severe (requiring withdrawal of treatment) and mild (not requiring withdrawal of treatment) adverse effects. Secondary outcomes included the proportion of patients who experienced at least one recurrence after the prophylaxis period, time to first

recurrence, proportion of patients with antibiotic resistant micro-organisms in future urine samples, and quality of life.

Data extraction and quality assessment

One reviewer (HA) extracted study characteristics (setting, participants, intervention, control, funding source) and outcome data from included trials. We contacted two authors for sub-group data on postmenopausal women. One author replied and provided relevant outcome data. Two reviewers (HA and SP) independently assessed the risk of bias of the included studies using the Cochrane Collaboration's risk of bias tool.[10] Disagreements were resolved through discussion. We used RevMan version 5.3 to meta-analyse the data and generate forest plots.

Data synthesis and analysis

Outcomes measured in only one trial were reported narratively. Outcomes measured in more than one trial were synthesised quantitatively. We estimated between trial heterogeneity using the I^2 statistic [11] and used random effects meta-analyses to estimate pooled risk ratios and 95% confidence intervals. [12] We undertook sensitivity analyses to examine treatment effects according to study quality and assessed the impact of including data from a potentially eligible trial where the study author did not reply to our request for data on older participants.

Results

From 6645 records, we identified 53 studies for full-text review (See Appendix 1). Four studies were eligible for inclusion.[13-16] Two studies recruited only postmenopausal women.[15] [16] Two studies recruited women of all ages but the

median age was >50 years.[13 14] For these studies, we contacted authors requesting data for postmenopausal women, or if menopausal status not ascertained, for women aged over 65. We received data from one author and hence included three trials consisting of 534 postmenopausal women in our review (Table 1).[14-16] We did not identify any studies that included older men.

Study ID	Setting	Population	Intervention	Control	Confirmation of UTI	Outcomes
Raz 2003	Outpatient infection disease clinics in Northern Israel	Community dwelling postmenopausal women with recurrent UTI[+]	Nitrofurantoin 100mg capsule at night for 9 months, with placebo vaginal pessary to mimic control group	Vaginal pessary containing 0.5mg Estriol daily for two weeks, then once a fortnight for nine months, with oral placebo capsules at night to mimic the intervention group	$>10^3$ colony forming units/mL bacteria in midstream urine	1.Number of women experiencing a recurrence during the prophylaxis period 2.Mean number of UTIs per woman during the prophylaxis period 3.Effects of oestrogens and antibiotics on vaginal mucosa, flora and pH 4.Mild and serious adverse events
Beerepoot 2012	Community setting in Amsterdam	Community dwelling postmenopausal women with a self-reported history of at least 3 UTIs in the preceding year	Trimethoprim-sulfamethoxazole 480mg tablet at night for 12 months, with placebo capsule twice daily	One capsule containing at least 10^9 colony forming units of *L rhamnosus GR-1* and *L reuteri RC-14* twice daily for 12 months, with placebo capsule at night	Symptoms +/- $>10^3$ colony forming units/mL bacteria in midstream urine	1.Number of women experiencing a recurrence during, and three months after the prophylaxis period 2.Mean number of UTIs per woman during the prophylaxis period 3.Median time to first recurrence during and after the prophylaxis period 4.Effects of lactobacilli and antibiotics on vaginal flora 5.Effects of lactobacilli and antibiotics on urinary and faecal antibiotic resistance 6.Mild and serious adverse events
Kranjcec 2014	Outpatients and primary care in Zabok, Croatia	Community dwelling women with self-reported recurrent UTI[+]	Nitrofurantoin 50mg at night for six months	Two grams D-mannose powder diluted in 200mls water at night for six months OR No treatment	Symptoms and $>10^3$ colony forming units/mL bacteria in midstream urine	1.Number of women experiencing a recurrence during the prophylaxis period 2.Median time to first recurrence during the prophylaxis period 3.Adverse events

Table1. Characteristics of included studies

† defined as two confirmed episodes of uncomplicated UTI in six months, or three in twelve months.

Trial characteristics

Trials were conducted in community and outpatient settings in Israel, Netherlands and Croatia. Only one trial included individuals with diabetes[16] and only one trial included individuals with renal impairment. [14] Intervention arms consisted of 6 to 12 months of antibiotic therapy. Control arms consisted of non-antibiotic prophylaxis with vaginal oestrogen pessaries[15], oral lactobacilli capsules[16], and D-mannose powder.[14] One trial reported the number of urinary tract infection recurrences per patient year during the prophylaxis period.[16] All trials reported the number of women experiencing a UTI during the prophylaxis period and frequency of adverse events. Only one trial assessed recurrence of UTI after the prophylaxis period (3 months).[16] One trial assessed effect on urinary and faecal bacterial resistance.[16]

Risk of bias

Figure 1 summarises the risk of bias assessment. Allocation and randomisation details were poorly reported in two trials.[14,15] One trial was assessed as high risk for performance and detection bias; trial arms consisted of an oral antibiotic capsule or D-mannose powder diluted in 200mls water or no treatment with no use of placebo and did not report on blinding of outcome assessors. [14] Only one trial reported a sample size calculation.[14] Overall, one trial was judged to be low risk of bias [16] and two trials unclear risk due to limited reporting of methods.[14,15]

Figure 1. Summary of risk of bias assessment

Effect of long-term antibiotics on recurrent UTI

Compared to a capsule of Lactobacilli, prophylaxis with 480mg of trimethoprim-sulfamethoxazole for 12 months led to fewer microbiologically confirmed UTI episodes per patient year (mean number of episodes per year = 1.2 versus 1.8, mean difference 0.6 , 95% confidence interval 0.0 to 1.4, *p*=0.02). Prophylaxis with trimethoprim-sulfamethoxazole also led to less women experiencing a microbiologically confirmed UTI during prophylaxis (49.4% versus 62.9%; RR 0.79, 95% confidence interval 0.63 to 1.0), and an increase in time to first UTI (six months versus three months; log-rank *p*=0.02). There was no difference between arms in the mean number of microbiologically confirmed UTI episodes three months after cessation of prophylaxis (mean number of episodes = 0.1 versus 0.2, mean difference 0.0, 95% confidence interval -0.1 to 0.3, *p*=0.64). [16]

Compared to vaginal oestrogen pessaries, prophylaxis with 100mg of nitrofurantoin for nine months led to fewer women experiencing a UTI during prophylaxis (42.3% versus 64.6%; RR 0.65, 95% confidence interval 0.8 to 0.90), and a lower mean number of UTI's per woman (0.6 episodes per woman versus 1.6 episodes per woman).[15]

Compared to D-mannose powder prophylaxis with 50mg of nitrofurantoin for six months led to more postmenopausal women experiencing a UTI during prophylaxis (24% versus 19%, RR 1.24, 95% confidence interval 0.57 to 2.69).[14]

Random effects meta-analysis (figure 2) shows long-term antibiotic therapy reduces the risk of a woman experiencing a UTI during the prophylaxis period (pooled Risk Ratio 0.76; 95% confidence interval 0.61 to 0.95) with about eight post-menopausal

women needing treatment with long-term antibiotics to prevent one woman experiencing a UTI during the prophylaxis period (NNT=8.5).

Figure 2. Forest plot showing results of meta-analysis for proportion of women experiencing a UTI during the prophylaxis period.

Adverse events

Commonly reported side effects across the three trials included skin rash, gastrointestinal disturbance and vaginal symptoms. There were no statistically significant difference between odds of adverse events between trimethoprim-sulfamethoxazole and lactobacilli [16], or between nitrofurantoin and vaginal oestrogens. [15] Risk of side effects with D-mannose powder was significantly lower than with nitrofurantoin (RR 0.28; 95% confidence interval 0.13 to 0.57).[14] Overall, absolute numbers of serious adverse events or events resulting in treatment withdrawal were small.

We had data on mild adverse events (not resulting in treatment withdrawal) for all three trials. There was marked heterogeneity between trials for adverse events (I^2 = 86%).

Meta-analyses showed no statistically significant difference between antibiotics and control for overall risk of mild adverse events (pooled RR 1.52; 95% confidence interval 0.76 to 3.03) (figure 3).

Figure 3. Forest plot showing results of meta-analysis for proportion of women experiencing mild side effect (treatment not withdrawn) during the prophylaxis period.

We extracted data for serious adverse events (resulting in treatment withdrawal) for two trials. Meta-analyses showed no statistically significant difference between antibiotics and control for overall risk of serious adverse events (pooled RR 0.90; 95% confidence interval 0.31 to 2.66; figure 4).

Figure 4. Forest plot showing results of meta-analysis for proportion of women experiencing a serious side effect (resulting in treatment withdrawal) during the prophylaxis period.

Effect of long-term antibiotic therapy on bacterial resistance

Compared with lactobacilli, women receiving 12 months prophylaxis with trimethoprim-sulfamethoxazole showed dramatic increases in the proportion of antibiotic resistant bacteria isolated from urine and faeces. For example, 20-40% of urinary and faecal E coli isolates were resistant to trimethoprim-sulfamethoxazole, trimethoprim and amoxicillin at baseline, increasing to 80-95% after one month of treatment. Over the 15 month follow-up period, resistance levels decreased following cessation of prophylaxis but remained above baseline levels.[16]

Sensitivity analyses

We assessed the impact of removing the study at high risk of bias on effect size and direction.[14] Removal made little difference to the meta-analysis for proportion of women experiencing a UTI during the prophylaxis period (pooled RR 0.74; 95% confidence interval 0.61 to 0.89). Removal did impact on the meta-analysis for proportion of women experiencing mild side effects during the prophylaxis period but

overall difference between antibiotics and placebo did not reach statistical significance (pooled RR 0.99, 95% confidence interval 0.82 to 1.20).

We also pooled aggregate data from another potentially relevant study where authors did not respond to our request for data regarding postmenopausal women/women over 65.[13] This study compared 500mg of cranberry extract to 100mg trimethoprim taken at night for six months. However, adding aggregate data for the whole study population (women aged 45 and above) to our meta-analysis for the proportion of women experiencing a UTI during the prophylaxis period made little difference to risk estimates (pooled RR 0.74; 95% confidence interval 0.61 to 0.90).

Discussion

Summary

This systematic review assessed evidence from three European randomised trials reported between 2003 and 2014. Trials only included women. Compared to controls, long-term prophylaxis with antibiotics reduced the risk of postmenopausal women experiencing a recurrent UTI during the prophylaxis period, without a statistically significant increase in risk of adverse events. Data from one trial [16] suggested this benefit was limited to duration of prophylaxis and was not apparent three months after cessation of prophylactic treatment. Data from one trial[16] showed long-term antibiotic prophylaxis dramatically increased urinary and faecal antibiotic resistance. However, trials were small with relatively short follow-up and had limitations in design and reporting, with one trial judged high risk for bias.

Strengths and limitations

We conducted this review following prospective registration of a review protocol and in line with guidance from the Cochrane handbook for systematic reviews of

interventions. Our search strategies was comprehensive and supplemented with reviews of reference lists of relevant trials[13-16], systematic reviews [8 17 18] and clinical guidelines. [19-21] We contacted authors where additional data were required for study inclusion. Due to resource constraints, we limited searches to English language and may have missed potentially relevant studies.

Comparison with existing literature

Meta-analysis of 10 randomised trials of women aged 18 and older found long-term antibiotics reduced the risk of UTI recurrence during the prophylaxis period by almost 80% (RR 0.21; 95% confidence interval 0.13 to 0.34; NNT = 1.85).[8] Our analyses showed a smaller effect size and greater NNT for postmenopausal women, possibly due to more complex pathophysiology of recurrent UTI in this population. We did not identify a statistically significant increase in risk of adverse events associated with use of antibiotics. Adverse events are often poorly reported in trials,[22] and we found heterogeneity for adverse events between trials. In addition, the studies included in this review compared long-term antibiotic therapy with various non-antibiotic treatments and not placebo, and this may have influenced effect sizes for adverse events towards the null. We found small absolute numbers of serious adverse events, and cannot exclude the possibility of important effects being missed in these relatively small studies.

During two point prevalence surveys, almost half of all adults residing in a sample of care homes were prescribed antibiotics for prevention of recurrent UTI.[1 2] Based on three small trials, with relatively short follow-up periods and design limitations, our meta-analyses suggest that this widely practiced use of prophylaxis reduces risk of recurrence in women. However, it is still unclear if these benefits extend to older men

or frailer care home populations. These are important gaps in current evidence, especially given large-scale observational data showing 10% of older men who experience an acute UTI go on to have at least one recurrence. [23]

Only one study followed up participants after cessation of prophylaxis and found that beneficial effects had ceased after 3 months.[16] Previous studies of younger women have reported similar findings suggesting that prophylaxis only confers protection from recurrence during the active prophylaxis phase.[8]

We found little data on the impact of long-term antibiotic therapy on antibiotic resistance. Antibiotic use is associated with increased risk of resistance.[3] Given the potential harms from acquiring an antibiotic resistant infection, the risk inferred by long-term antibiotic use is an important factor to consider with patients when making decisions about antibiotic prophylaxis.

Implications for research and practice

Based on the data we analysed, a pragmatic approach is required when considering prescribing long-term antibiotics in older patients with recurrent UTI. Although long-term antibiotics may reduce the risk of UTI recurrence in women, this benefit diminishes upon cessation of treatment. Little is known about optimal prophylaxis period, long-term effects on health, risk of antibiotic resistant infections, effect in older men, effect in frail care home residents, or impact on important patient centred outcomes. These unknowns must be balanced against benefits and patient preferences.

Future research efforts on recurrent UTI should focus on improving the design and reporting of trials and developing a core set of outcomes to allow better synthesis of trial data. Antibiotic prophylaxis should be compared with non-antibiotic prophylaxis

with some evidence of efficacy (such as vaginal oestrogens) rather than those with little or poor evidence of efficacy. Researchers should address unanswered questions regarding long-term effects, duration of use, adverse effects and antibiotic resistance.

Conclusion

There is ongoing uncertainty around the benefits and harms of long-term antibiotics in older men and frail care home residents with recurrent UTI. Prescribing long-term antibiotics to older women with recurrent UTI needs careful discussion between patient and clinician of reduced risk of relapse, potential increases in urinary and faecal antibiotic resistance and rapidly diminished benefit once prophylaxis stops.

Acknowledgements

We thank Bojana Kranjčec, Dino Papeš, and Silvio Altarac for providing requested data.

Funding

This report is independent research arising from a National Institute of Health Research (NIHR) Doctoral Research Fellowship awarded to Haroon Ahmed, and supported by Health and Care Research Wales (HCRW). The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS Wales, HCRW or the Welsh Government. The funders had no role in the design or preparation or this manuscript.

Competing interests

All authors have completed the ICMJE uniform disclosure form atwww.icmje.org/coi_disclosure.pdf and declare: no support from any organisation

for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Author contributions

HA, CB, NF, DF and SP conceived and designed the study. HA and FD did the searches. HA, FD and SP assessed studies for inclusion and risk of bias and extracted relevant data. HA wrote the first draft of the manuscript. All authors contributed to further drafts and final manuscript.

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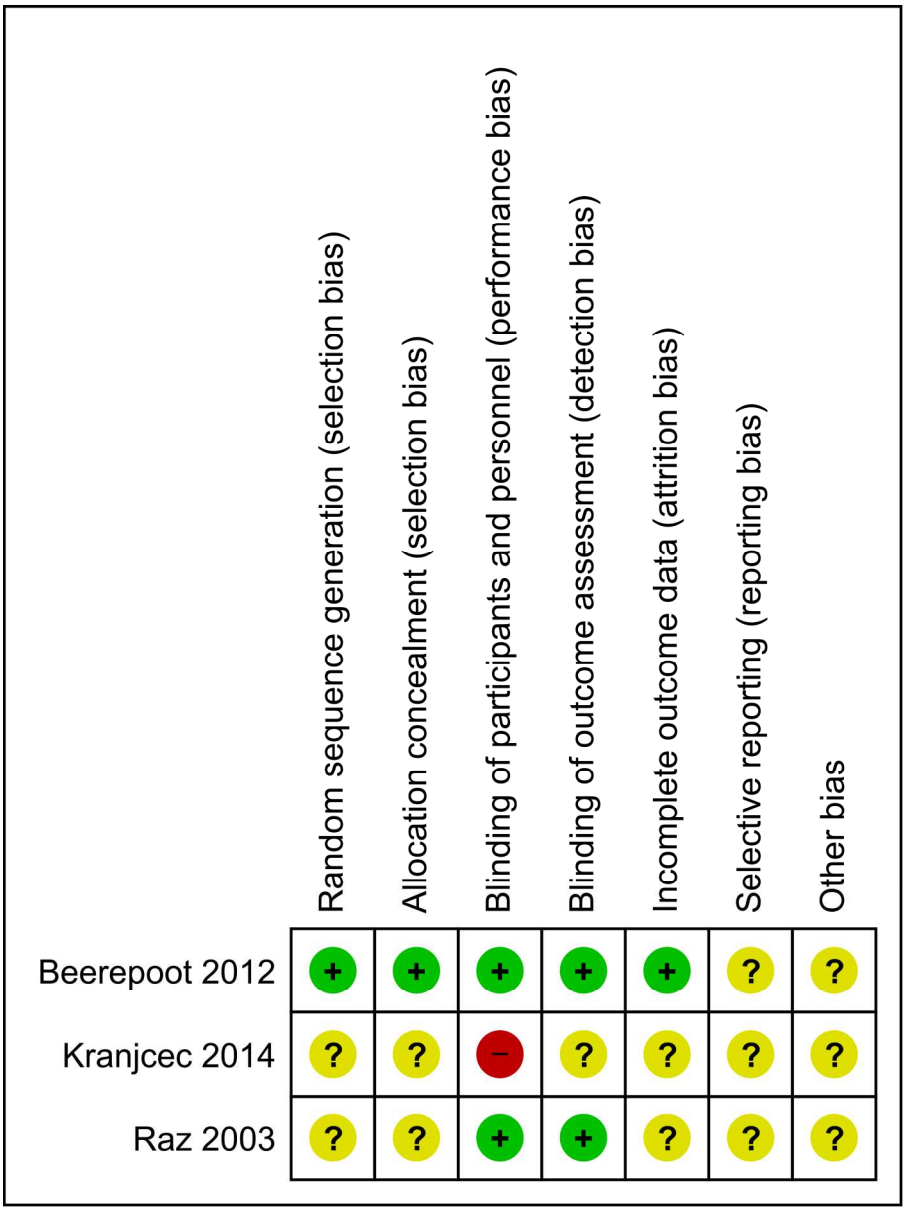


Figure 1. Summary of risk of bias assessment

231x309mm (300 x 300 DPI)

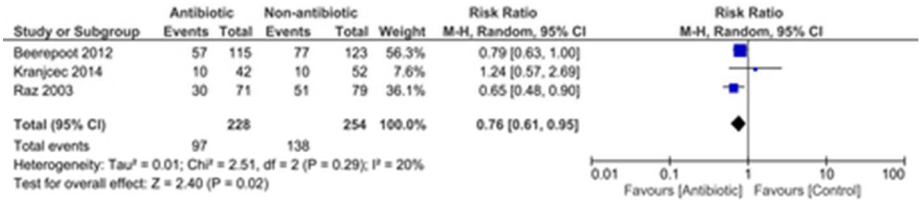


Figure 2. Forest plot showing results of meta-analysis for proportion of women experiencing a UTI during the prophylaxis period.

38x8mm (300 x 300 DPI)

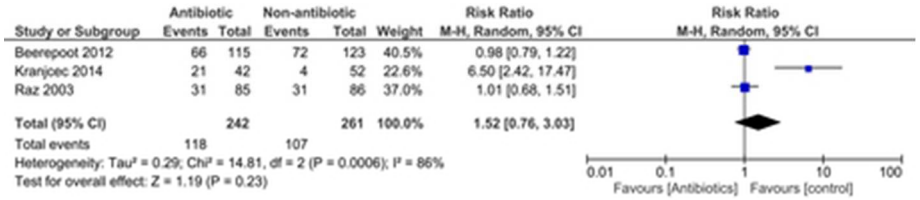


Figure 3. Forest plot showing results of meta-analysis for proportion of women experiencing mild side effect (treatment not withdrawn) during the prophylaxis period.

38x8mm (300 x 300 DPI)

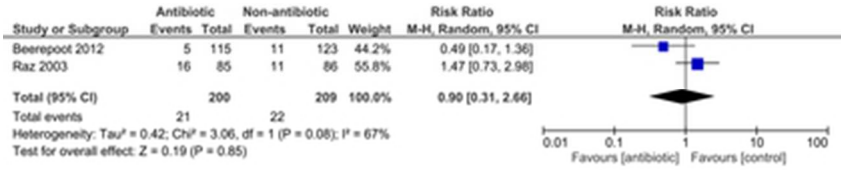
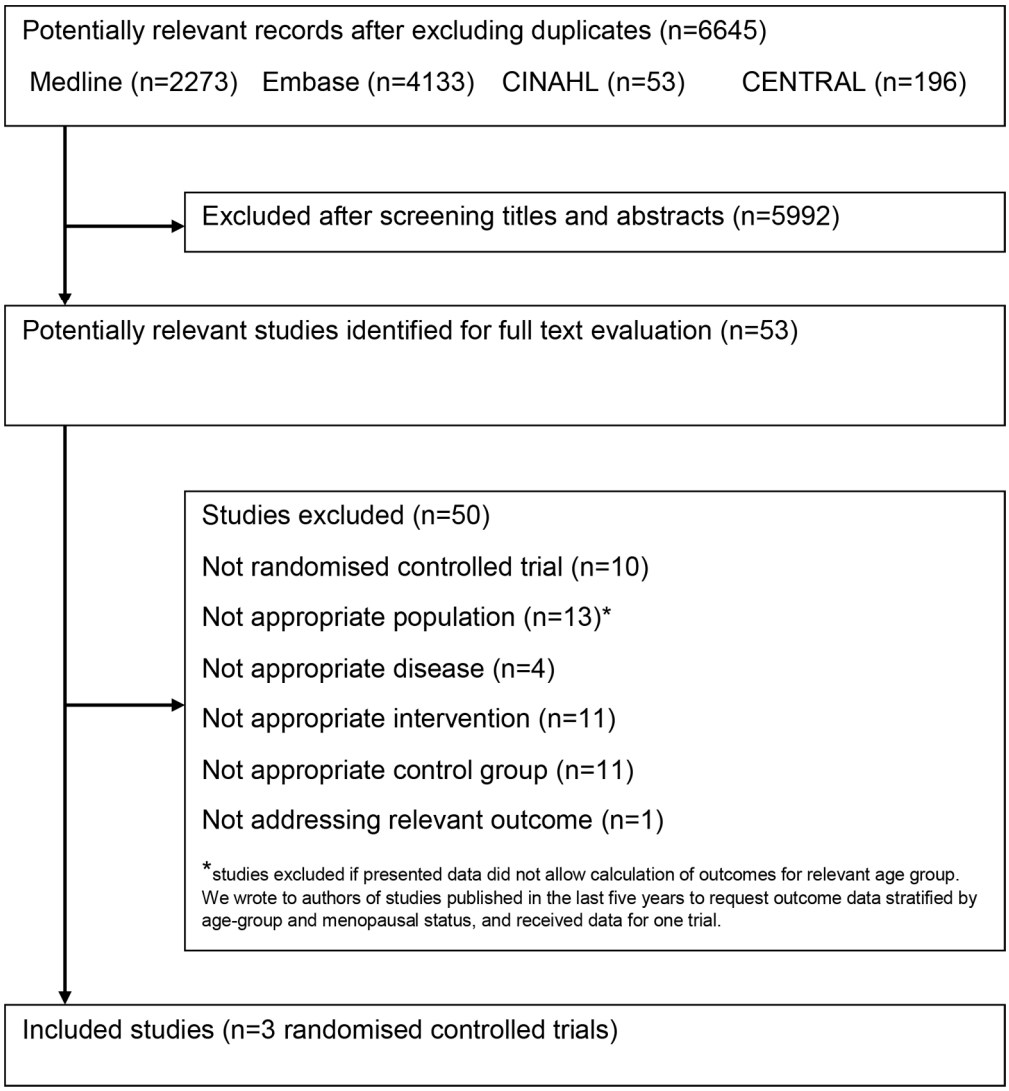


Figure 4. Forest plot showing results of meta-analysis for proportion of women experiencing a serious side effect (resulting in treatment withdrawal) during the prophylaxis period.

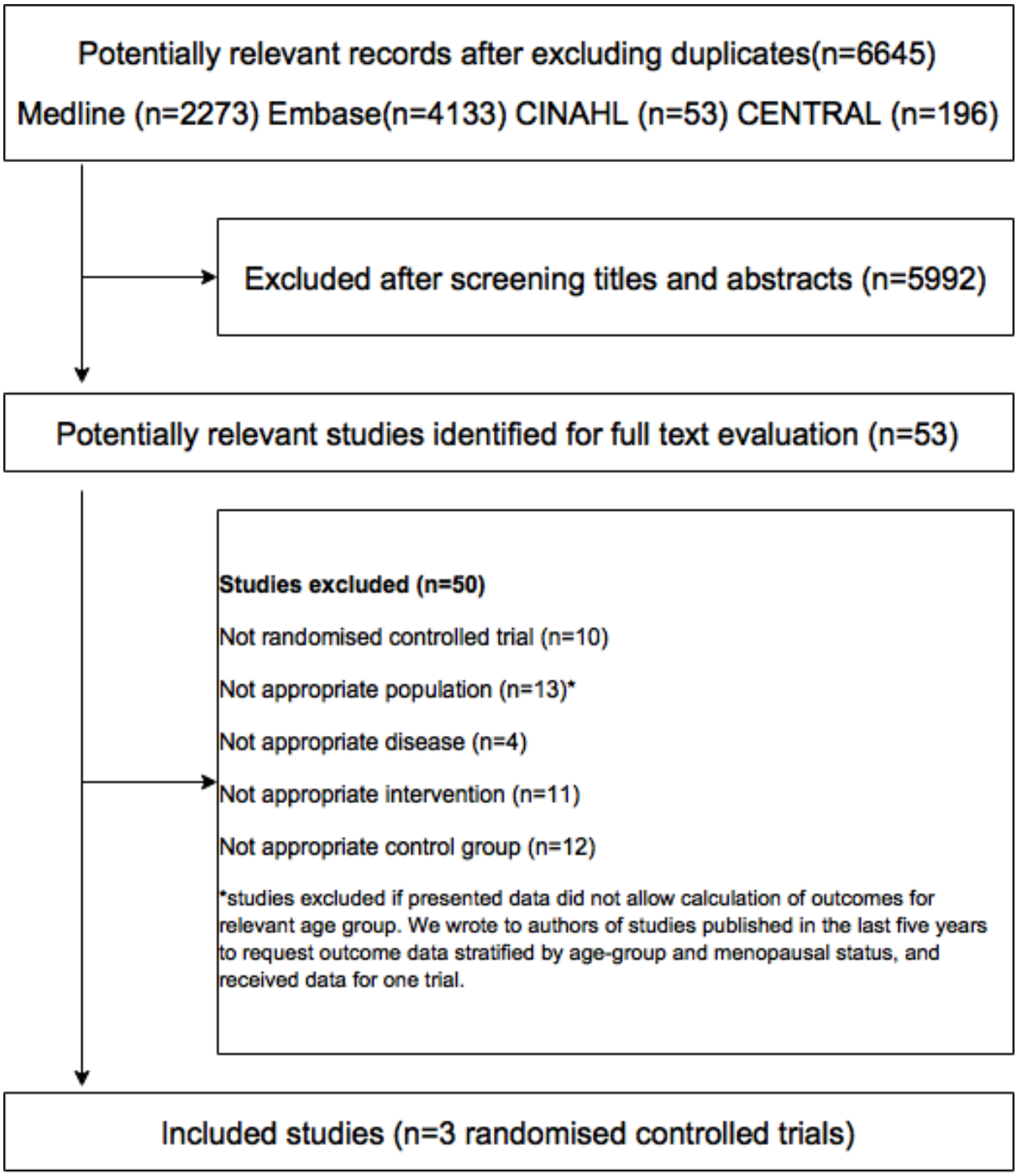
35x7mm (300 x 300 DPI)



Appendix 1: PRISMA flowchart

159x171mm (300 x 300 DPI)

Appendix 1. PRISMA flowchart



Appendix 2. Medline Search strategy

1. exp Urinary Tract Infections/
2. Urinary Tract Infection*.mp.
3. exp Cystitis/
4. (bladder adj infection*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. Bacteriuria.mp.
6. Pyuria.mp.
7. (recurrent adj urinary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. UTI.mp.
9. exp Anti-Bacterial Agents/ or exp Antibiotic Prophylaxis/
10. antimicrobial*.mp.
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. randomized.ab.
14. placebo.ab.
15. clinical trials as topic.sh.
16. randomly.ab.
17. trial.ti.
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
19. 9 or 10
20. 18 and 19
21. 11 or 12 or 13 or 14 or 15 or 16 or 17
22. exp animals/ not humans.sh.
23. 21 not 22
24. 20 and 23

Text S1 - Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3 and 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix2

Section/topic	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Appendix1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Figure1 page 11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and	12-14

Section/topic	#	Checklist item	Reported on page #
		confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure1 page 11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression) (see Item 16).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING1			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19